

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
3 January 2002 (03.01.2002)

PCT

(10) International Publication Number
WO 02/00627 A1

(51) International Patent Classification⁷: C07D 231/12, A61K 31/415

(21) International Application Number: PCT/TR01/00025

(22) International Filing Date: 26 June 2001 (26.06.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2000/01872 26 June 2000 (26.06.2000) TR

(71) Applicant (for all designated States except US): **FAKO ILACLARI A.S.** [TR/TR]; Buyukdere Caddesi No: 205, 4. Levent, 80650 Istanbul (TR).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **GUNDUZ, A.**, Halit [TR/TR]; **FAKO ILACLARI A.S.**, Buyukdere Caddesi No:205, 4. Levent, 80650 Istanbul (TR). **GOKTEPE, Mehmet** [TR/TR]; **FAKO ILACLARI A.S.**, Buyukdere Caddesi No:205, 4. Levent, 80650 Istanbul (TR). **BAHAR, Mehmet** [TR/TR]; **FAKO ILACLARI A.S.**, Buyukdere Caddesi No:205, 4. Levent, 80650 Istanbul (TR).

(74) Agent: **AKSOY DANISMANLIK GIDA TEKSTIL ITHALAT IHRACAT TICARET LTD. STI.**; 1. Cadde 5/6, Bahcelievler, 06500 Ankara (TR).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

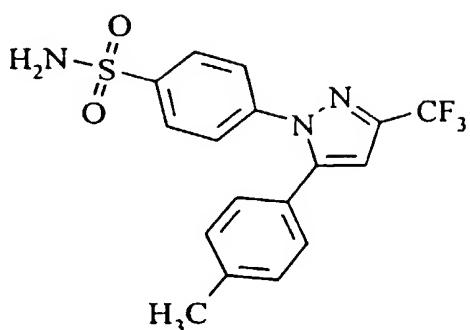
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: A CRYSTALLINE FORM OF CELECOXIB



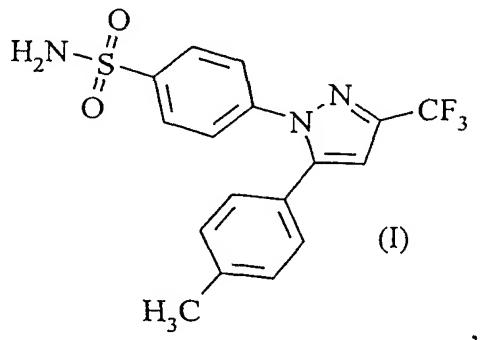
(I)

(57) Abstract: A new crystalline form of 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide of Formula (I), designated as Form I and a method for its production.

WO 02/00627 A1

A CRYSTALLINE FORM OF CELECOXIB

This invention relates to the pharmaceutical therapeutic agent 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (celecoxib) of formula I



specifically to a new crystalline form of celecoxib with improved properties. This invention further relates to a method for the production of this crystalline form of the agent.

Since prostaglandins play a major role in the inflammation process, the discovery of non-steroidal anti-inflammatory drugs (NSAIDs) has focused on the inhibition of prostaglandin production, especially PGG₂, PGH₂ and PGC₂ production. The use of NSAIDs in the treatment of pain and swelling associated with the inflammation tends to cause side effects by affecting other prostaglandin regulated processes. Thus NSAIDs tend to cause significant side effects including ulcers.

Previous NSAIDs have been found to inhibit some enzymes including cyclooxygenase. Recently, an inducible form of cyclooxygenase associated with inflammation known as cyclooxygenase II (COX-2) or prostaglandin G/M synthase II has been found to exist. This enzyme is more effective in reducing inflammation, causing fewer and less drastic side effects.

Several compounds selectively inhibiting cyclooxygenase II are described in U.S. Patent Nos. 5 380 738, 5 344 991, 5 393 790, 5 466 823, 5 434 178, 5 474 995, 5 510 368, and International Applications WO 96/06840, 96/03388, 96/03387, 95/15316, 94/15932, 94/27980, 95/00501, 94/13635, 94/20480 and 94/26731.

Certain substituted pyrazolylbenzenesulfonamides, specifically celecoxib (4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide) as selective COX-2 inhibitor and their preparation have been described in International Application WO 95/15316. In addition, an efficient preparation of 3-haloalkyl-1H-pyrazoles in a one-pot synthesis which is suitable for large-scale process has been described in International Application WO 96/37476.

International Application No. WO 00/32189 discloses specific celecoxib compositions. In this document a number of problems concerning the formulation of this agent, inter alia, its cohesiveness, low bulk density, low compressibility, poor solubility, etc., are described. According to this document, these disadvantages are caused by the crystal structure of celecoxib. Unformulated celecoxib, which has a crystal morphology that tends to form long cohesive needles, typically fuses into a monolith mass upon compression in a tablet die, which leads to problems in blending the agent uniformly. Further, low bulk density causes problems in processing the small quantities required in the formulation of pharmaceutical compositions.

It has now surprisingly been discovered that celecoxib may exist at least in two crystalline forms, hereinafter designated as Form I and Form II, having different properties.

Certain organic compounds can exist in several different crystal forms, which can have different chemical and physical properties, such as density, hardness, flow properties, etc. Therefore, new crystal forms of existing compounds are of great interest.

The new crystal form of celecoxib reported herein provides improved properties, making it possible to overcome the problems described in the prior art. Since the new crystal form does not have the disadvantages of the known needle-like crystals, it overcomes the problems disclosed e.g. in WO 00/32189.

The object of the present invention, therefore, is to provide a new crystalline form of celecoxib which avoids the problems produced by the known, needle-like crystalline form.

The solution of this object is provided by the new crystalline form of celecoxib as disclosed herein, which we have called "Form I" of celecoxib, and by the corresponding production method, as also described herein.

Crystalline forms are characterised by means of X-ray powder diffraction patterns. For this purpose a PHILIPS PW 1710 based diffractometer was used and Cu-K_α-radiation (λ (Cu-K_{α1}) = 1.54056 Å; λ (Cu-K_{α2}) = 1.54439 Å) was applied. X-ray diffraction data are provided in terms of 2θ values and corresponding intensities.

The crystalline form of celecoxib designated as Form I according to the present invention is characterised by at least the X-ray powder diffractogram data given in table I:

TABLE I: X-ray Diffraction data of Form I:

Angle [°2θ]	Rel.int [%]
14.800	69.0
16.050	78.9
17.875	63.7
19.615	100.0
21.455	96.6
22.080	68.1
22.385	65.4
23.425	62.5
25.330	64.5
29.355	60.8

In a preferred embodiment of the present invention said crystalline form of 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide of Form I is further

characterised by at least the following further X-ray powder diffractogram data given in table II:

TABLE II: Further X-ray Diffraction data of Form I:

Angle [°2θ]	Rel.int [%]
10.670	33.4
10.970	34.0
12.985	32.4
13.855	17.5
18.340	40.4
18.685	40.0
20.425	19.1
20.670	19.0
23.185	48.7
24.510	37.8
24.930	34.5
25.730	22.8
26.915	23.1
27.630	31.5
28.185	26.2
29.955	32.7
30.375	9.9
31.405	9.6
34.915	15.7
35.585	10.9
37.895	17.9
44.070	9.4
45.250	14.5

(in addition to the dominant reflexes of table I).

An example of the X-ray diffraction pattern of Form I is shown in Fig. 1.

The alternative disadvantageous, needle-like crystal form (designated herein as Form II) which is provided by the methods described in the prior art differs significantly from Form I according to the present invention.

An example of the X-ray diffraction pattern for the known Form II is shown in fig. 2 and the corresponding data are given in Table III.

TABLE III: X-ray Diffraction data of Form II

Angle [°2θ]	Rel.int [%]
11.025	27.5
13.285	5.9
15.115	16.5
16.415	91.4
17.625	3.2
18.265	3.6
19.785	5.6
21.820	100.00
22.440	16.9
23.500	2.7
24.620	3.0
25.460	2.7
27.280	21.0
29.885	15.6
31.580	1.5
32.815	9.0
35.185	7.4
38.205	5.8
38.415	4.2
39.695	2.5
40.740	3.7
41.285	0.8
42.960	2.4
43.810	2.7
44.820	4.5
45.415	5.0
46.300	4.9

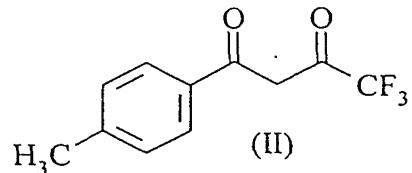
Further, SEM images of the crystallites of Form I according to the invention and Form II obtained by the production methods known in the prior art clearly illustrate the plate like habit of the crystals of Form I in contrast to the needle like habit of the crystals of Form II; as is illustrated by attached Fig. 3 and 4.

One of the main disadvantages of the needle-like crystals of Form II mentioned in WO 00/32189 is their low bulk density. It was found, that the crystals of the invention's Form I are distinctly denser in comparison to the crystals of Form II prepared according to the methods as given in International Applications WO 95/15316 and WO 96/37476. The following densities are typical and characteristic for the crystals of Form I and II, respectively:

	Form I	Form II
bulk density	\geq about 0.270 g/ml	about 0.130 g/ml
tap density	\geq about 0.360 g/ml	about 0.180 g/ml

Consequently, the crystals of Form I are denser than the crystals of Form II, providing improved filtration and drying characteristics. Due to its increased density, better flow properties and lower electrostatic charge, Form I provides further advantages in formulation and capsule preparation.

The present invention further relates to a method for the production of the crystals of Form I of celecoxib by reacting 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione of formula II



with 4-sulphonamidophenylhydrazine hydrochloride in a suitable solvent, crystallizing the resulting 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide from the reaction mixture and recrystallizing it from a suitable solvent.

1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione may be prepared according to Example 2 Step 1 in International Application WO 95/15316.

The preparation of celecoxib, according to the present invention, differs from the production described in WO 95/15316 mainly by the crystallization system used.

Thus, the dione is preferably reacted with 4-sulphonamidophenylhydrazine hydrochloride in isopropanol, instead of absolute ethanol, at reflux temperature. The reaction mixture is treated with activated carbon; after filtering, the product is preferably obtained by crystallizing it by the addition of a non-solvent, especially water (instead of by concentration of the reaction mixture). Finally, the substance is preferably recrystallized from isopropanol and water, instead of methylenechloride/hexane.

Accordingly, the present invention provides further advantages for the preparation of celecoxib by eliminating methylene chloride, a risk for the environment and human health. In addition, it also eliminates the use of n-hexane which causes an ignition and fire risk due to its electrostatic charge accumulation property. Further, according to the present invention, water replaces n-hexane. The use of isopropanol is a further advantage, since it is commercially available and widely used in chemical industry compared to absolute ethanol. Isopropanol should be anhydrous and may be combined with other hydroxylic solvents. Finally, by precipitating the product from the reaction mixture instead of concentrating the reaction mixture to dryness, a higher purity is achieved.

In order to obtain crystals of Form I, celecoxib is most preferably prepared by dissolving celecoxib in a suitable solvent system comprising at least one amide solvent, preferably selected from the group comprising N,N-dimethylformamide, NN-dimethylacetamide and/or mixtures thereof, N,N-dimethylformamide being most preferred, from which solution the crystals of Form I are obtained by the addition of a non-solvent, especially water.

This recrystallization is generally carried out at temperatures of 0 to 80 °C, particularly of 5 to 70 °C, preferably of 10 to 60 °C, more preferably of 15 to 50 °C, most preferably of 20 to 40 °C, e.g., of 25 to 30 °C and/or ambient temperature.

The present invention further includes crystalline celecoxib of Form I crystallography, obtainable by the above described method of production.

Further, the present invention includes pharmaceutical preparations, comprising crystalline celecoxib according to the present invention. Pharmaceutical preparations according to the present invention may be adapted for oral administration and are conveniently presented in the form of, e.g., tablets, capsules, dragees or the like. The formulations may contain ingredients like pharmaceutically acceptable carriers, excipients, adjuvants, etc. as they are known in the art.

Example

Step a: 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione

4'-Methylacetophenone was dissolved in methanol (25 ml) under nitrogen atmosphere. To the stirred solution was added 25% sodium methoxide in methanol (12 ml). The reaction mixture was stirred for 5 minutes and ethyltrifluoroacetate (5.5ml) was added. After refluxing under nitrogen atmosphere for 24 hours the mixture was cooled to room temperature and concentrated. 10 % hydrochloric acid (100 ml) was added. The mixture was extracted with ethyl acetate (4 x 75 ml). The combined organic layer was dried over MgSO₄, filtered and concentrated. The product was obtained as an oily residue.

Step b: 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

1-(4-Methylphenyl)-4,4,4-trifluorobutane-1,3-dione (4.14 g) from step a was stirred in isopropanol (75 ml). 4-sulphonamidophenylhydrazine hydrochloride (4.25 g) was added. The reaction mixture was refluxed under nitrogen atmosphere for 24 hours, cooled to room temperature and filtered, The filtrate was treated with activated carbon at 40–45° C. The product was crystallized by adding water (150 ml). The product was recrystallized from isopropanol and water.

Step c: Isolation of Form I

4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (20 g) from step b was dissolved in N,N-dimethylformamide (80 ml) at room temperature. The product was crystallized by addition of water (200 ml). The reaction mixture was stirred for 30 minutes. The product was isolated by filtration, washed with water (3 x 40 ml) and dried.
Yield: 18 g.

It corresponded to fig. 3 and showed the X-ray diffraction data presented in fig. 1 and tables I and II.

CLAIMS

1. Crystalline 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, characterised by at least the following X-ray powder diffractogram reflexes:

Angle [°2θ]	Rel.int [%]
14.800	69.0
16.050	78.9
17.875	63.7
19.615	100.0
21.455	96.6
22.080	68.1
22.385	65.4
23.425	62.5
25.330	64.5
29.355	60.8

2. The crystalline 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide according to claim 1, characterised by at least the following further X-ray powder diffractogram reflexes:

Angle [°2θ]	Rel.int [%]
10.670	33.4
10.970	34.0
12.985	32.4
13.855	17.5
18.340	40.4
18.685	40.0
20.425	19.1
20.670	19.0
23.185	48.7
24.510	37.8
24.930	34.5
25.730	22.8
26.915	23.1
27.630	31.5
28.185	26.2
29.955	32.7
30.375	9.9
31.405	9.6
34.915	15.7
35.585	10.9
37.895	17.9
44.070	9.4
45.250	14.5

3. Crystalline 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, especially according to claim 1 or 2,
characterised in that it has
a tap density of not less than 0.360 g/ml, and/or
a bulk density of not less than 0.270 g/ml.

4. A method for the production of the crystalline substance according to any one of claims 1 to 3,

characterised in that 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione is reacted with 4-sulphonamidophenylhydrazine hydrochloride in a suitable solvent, the resulting 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide is crystallized from the reaction mixture and is recrystallized by solvent precipitation from a suitable solvent.

5. The method according to claim 4,

characterised in that the reaction is carried out in isopropanol.

6. The method according to any one of claims 4 or 5,

characterised in that 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide is crystallized from the reaction mixture by the addition of a non-solvent, especially water.

7. The method according to any one of claims 4 to 6,

characterised in that 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide is recrystallized from a solvent system comprising at least one amide solvent.

8. The method according to any one of claims 4 to 7,

characterised in that 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide is recrystallized from a solvent system comprising at least one amide solvent by addition of a non-solvent, especially water, at a temperature between 0°C and 80°C.

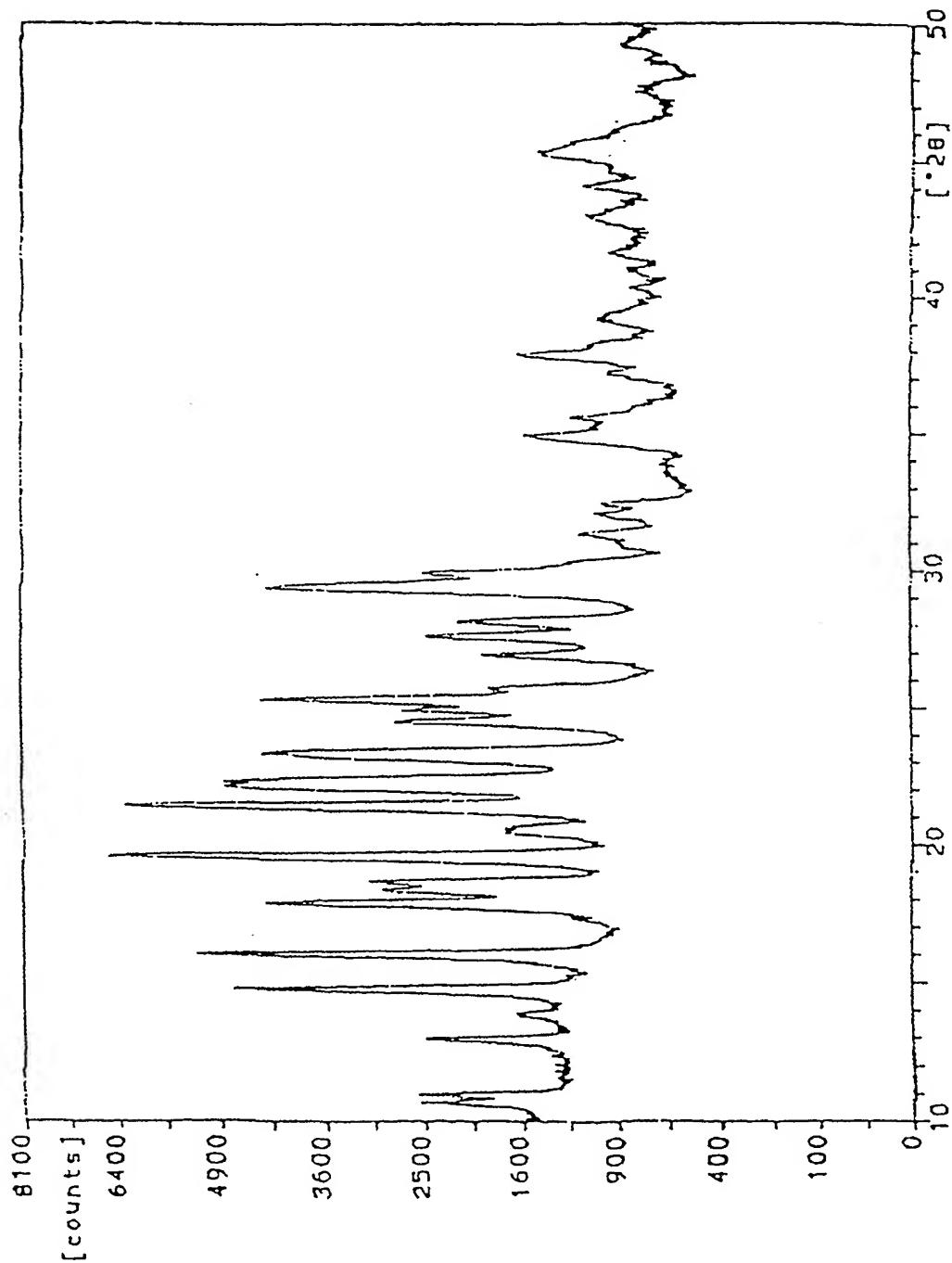
9. The method according to any one of claims 4 to 8,
characterised in that the amide solvent is selected from the group, comprising N,N-dimethylformamide, N,N-dimethylacetamide and mixtures thereof.

10. Crystalline 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide in accordance with claims 1,2 or 3, obtainable by the method of any one of claims 4 to 8.

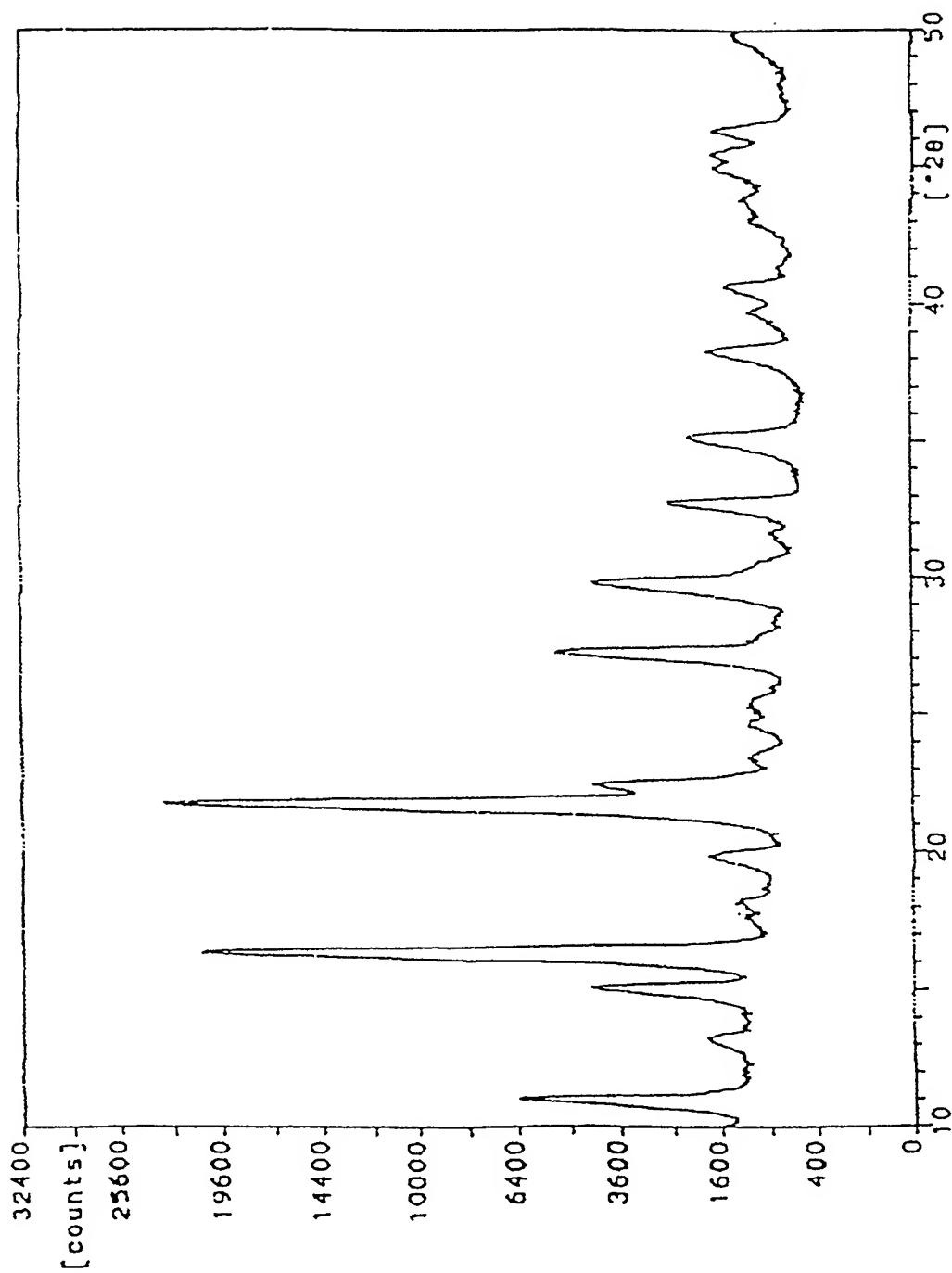
11. A pharmaceutical preparation, comprising crystalline 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide in accordance with any one of claims 1,2,3 or 10.

1 / 5

Figure I



2 / 5

Figure 2

3 / 5

Figure 3: SEM image illustrating the plate like habit of the crystals of Form I:

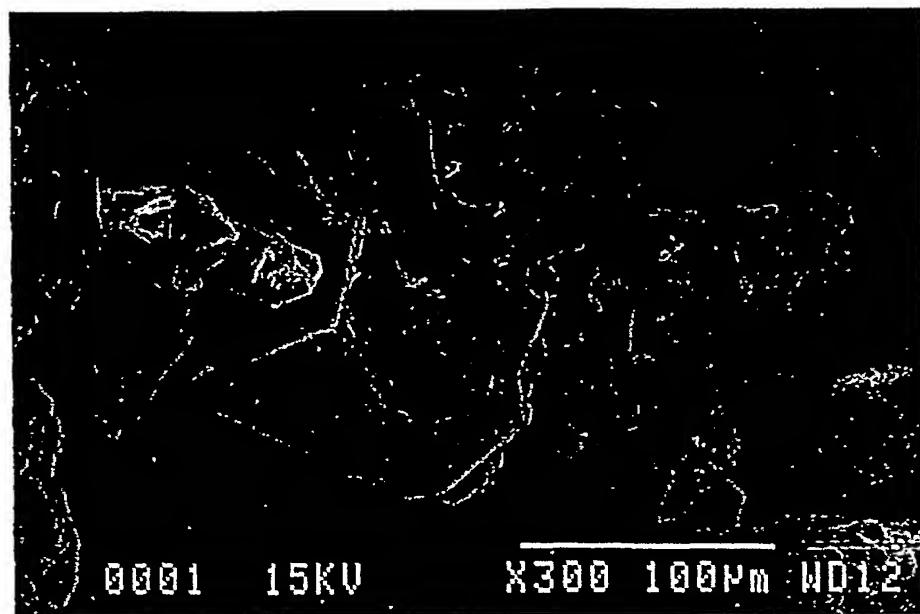


Figure 3

4 / 5

Figure 4: SEM image illustrating the needle like habit of crystals of Form II:

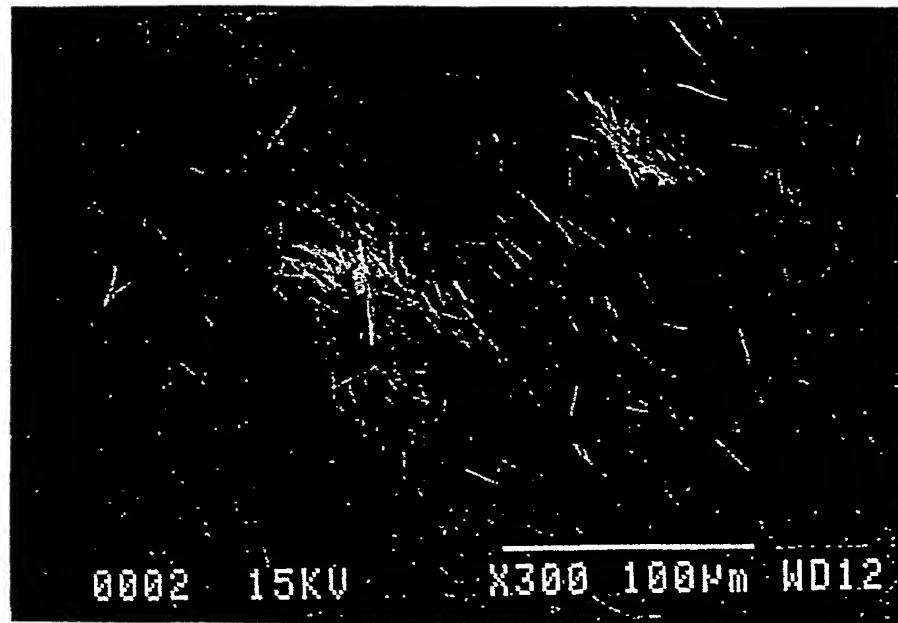
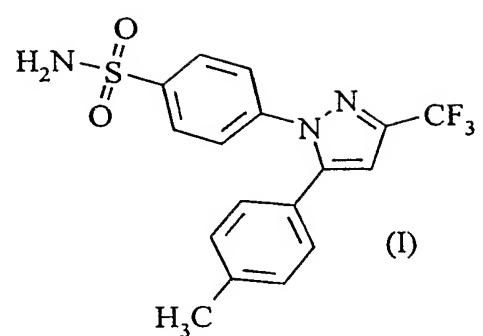


Figure 4

5 / 5

Figure 5

INTERNATIONAL SEARCH REPORT

Int	ional Application No
PCT/TR 01/00025	

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07D231/12 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 37476 A (SEARLE) 28 November 1996 (1996-11-28) example 1 ---	1-11
X	WO 95 15316 A (GRANETS MATTHEW J ;MIYASHIRO JULIE M (US); SEARLE & CO (US); TALLE) 8 June 1995 (1995-06-08) page 64 -page 65, line 7; example 2 ---	1-11 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

26 September 2001

02/10/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

De Jong, B

INTERNATIONAL SEARCH REPORT

Int	ional Application No
PCT/TR	01/00025

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PENNING, THOMAS D. ET AL: "Synthesis and Biological Evaluation of the 1,5-Diarylpyrazole Class of Cyclooxygenase-2 Inhibitors: Identification of 4-'5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl!benzenesulfonamide (SC-58635, Celecoxib)" J. MED. CHEM. (1997), 40(9), 1347-1365 , XP002114833 page 1356, left-hand column, line 18 - line 29 ---	1-3,10, 11
P,X	WO 01 42222 A (MIYAKE PATRICIA J ;FERRO LEONARD J (IL); PHARMACIA CORP (US)) 14 June 2001 (2001-06-14) page 4 -page 5; example 2 page 11 -page 14 page 52 -page 57 ---	1-11
P,X	WO 00 42021 A (MERCK FROSST CANADA INC ;TILLYER RICHARD D (CA); DALTON CHAD (CA);) 20 July 2000 (2000-07-20) page 4; claim 7; example 1 -----	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Application No

PCT/TR 01/00025

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9637476	A 28-11-1996	AU 708964 B2 AU 5873696 A BR 9609043 A CA 2222138 A1 CN 1190960 A CZ 9703689 A3 EP 0828717 A1 JP 11505848 T NO 975387 A NZ 308875 A PL 323492 A1 WO 9637476 A1 US 5910597 A US 5892053 A	19-08-1999 11-12-1996 23-02-1999 28-11-1996 19-08-1998 18-03-1998 18-03-1998 25-05-1999 17-12-1997 30-08-1999 30-03-1998 28-11-1996 08-06-1999 06-04-1999
WO 9515316	A 08-06-1995	US 5466823 A US 5521207 A AT 187965 T AU 690609 B2 AU 1171495 A BR 1100406 A3 CA 2177576 A1 CN 1141630 A , B CN 1280125 A CN 1280126 A CZ 9601503 A3 DE 69422306 D1 DE 69422306 T2 DK 731795 T3 EP 0731795 A1 EP 0924201 A1 EP 0922697 A1 EP 0923933 A1 ES 2141916 T3 FI 962249 A GR 3032696 T3 HK 1013649 A1 HU 74180 A2 JP 2000109466 A JP 3025017 B2 JP 9506350 T KR 229343 B1 KR 263817 B1 KR 261669 B1 LU 90698 A9 NO 962184 A NZ 276885 A PL 314695 A1 PT 731795 T RU 2139281 C1 WO 9515316 A1 US 6156781 A US 5510496 A US 5563165 A US 5508426 A US 5516907 A US 5504215 A US 5753688 A	14-11-1995 28-05-1996 15-01-2000 30-04-1998 19-06-1995 08-02-2000 08-06-1995 29-01-1997 17-01-2001 17-01-2001 11-12-1996 27-01-2000 18-05-2000 15-05-2000 18-09-1996 23-06-1999 16-06-1999 23-06-1999 01-04-2000 29-05-1996 30-06-2000 07-07-2000 28-11-1996 18-04-2000 27-03-2000 24-06-1997 01-11-1999 16-08-2000 15-07-2000 13-02-2001 29-05-1996 30-08-1999 16-09-1996 31-05-2000 10-10-1999 08-06-1995 05-12-2000 23-04-1996 08-10-1996 16-04-1996 14-05-1996 02-04-1996 19-05-1998

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Application No
PCT/TR 01/00025

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
WO 9515316	A		US 5760068 A ZA 9409418 A	02-06-1998 28-11-1995
WO 0142222	A	14-06-2001	WO 0141536 A2 WO 0141761 A2 WO 0141762 A2 WO 0141760 A2 WO 0142221 A1 WO 0142222 A1	14-06-2001 14-06-2001 14-06-2001 14-06-2001 14-06-2001 14-06-2001
WO 0042021	A	20-07-2000	AU 3028500 A WO 0042021 A1 US 6150534 A US 6232472 B1	01-08-2000 20-07-2000 21-11-2000 15-05-2001